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DAE/1648/11  
#48

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ) Art Unit: 1643  
CLASSEN, John B. ) Examiner: B. BRUMBACK  
Appln. No.: 08/591,651 ) Washington, D.C.  
Date Filed: February 12, 1996 ) December 12, 2002  
For: METHOD AND COMPOSITION FOR ) DOCKET: CLASSEN=1A  
AN EARLY VACCINE TO PROTECT )  
AGAINST BOTH COMMON... ) Confirmation No.: 9417

**REQUEST FOR RECONSIDERATION AND CONDITIONAL "NO-FEE"**  
**PETITION FOR SUPERVISORY REVIEW UNDER 37 C.F.R. §1.181, AND**  
**CONDITIONAL PETITION TO WAIVE THE RULES UNDER 37 CFR §1.183**

Honorable Commissioner for Patents  
Washington, D.C. 20231

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S i r:

TECH CENTER 1600/2900

We are requesting the supervisory patent examiner to reconsider the November 18, 2002 advisory action, denying entry of the declaration and exhibits filed October 18, 2002, in view of the supplemental showing under 37 CFR §§1.116 and 1.195 made herein.

If this request is denied, then we ask that this paper be considered a petition for supervisory review under 37 CFR §1.181 and referred to the Group Director. If that petition is denied in whole or in part, Applicant petitions to the Commissioner under 37 CFR §1.183.

Background

An Appeal Brief was initially filed in this case on May 1, 2000. Rather than file an answer, the Examiner reopened prosecution, making, *inter alia*, an enablement rejection.

In support of the rejection, the Examiner initially cited just "PIDJ" and "Boumpas" (see June 20, 2000 action, pages 9-

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10). The February 21, 2001 action additionally relied on DeStefano (ref. DU), EURODIAB (ref. EB), Graves (ref. EF), Heijbel (ref. EI), Hiltunen (ref. EL), Jefferson (ref. EQ), Karvonen (ref. EV), Bedford (ref. HD), Petousis-Harris (ref. HE), Dahlquist (ref. HK), Jefferson T.O. (ref. HP), Elliott (ref. IJ), and Anonymous (ref. IN)<sup>1</sup>, but confined itself to a general allegation that these teach a lack of association between immunization schedules and type 1 diabetes. There was no specific analysis of any of these references.

Finally, in the final rejection mailed November 5, 2001, the Examiner argued that a "Classen and Classen reference" submitted by Applicant on August 17, 2001 in fact supported the enablement rejection. There were two Classen and Classen references filed that day, "Clustering of Cases...." and "Large Decline...."

On October 18, 2002, Applicants filed a "Supplemental Amendment After Final Rejection and Submission of New Evidence", and a "Declaration (II) of Dr. Bart Classen", with attached exhibits. The Declaration discussed several pertinent references that had been published after the maildate of the final rejection, as well as the references first relied on in the February 21, 2001 action. It enclosed copies of the newly discovered references, as well as some other supporting documents discussed in detail below. A new Appellant's Brief was filed on November 5, 2002.

On November 18, 2002, the PTO mailed an advisory action which (1) entered the October 18, 2002 amendments to the claims, and (2) refused entry of the Declaration and exhibits.

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<sup>1</sup> These references were made of record by the February 1, 2002 IDS and discussed in an exhibit, "Scientific Evidence", filed December 19, 2000.

The PTO explained

Submission of evidence after a final action is governed by 37 C.F.R. § 1.116. This rule requires applicant to provide good and sufficient reasons as to why the submissions are necessary and were not earlier presented. In this case, the Declaration of Dr. Classen will not be considered because the Declaration is based in part upon the consideration of newly cited art references. Applicant has not provided the statements regarding the newly cited references required under 37 C.F.R. § 1.97(e). In addition, the arguments of the Declaration are not limited to the alleged newly discovered references. The applicant has not made the showings required under 37 C.F.R. § 1.116 required for these arguments.

Reconsideration of this refusal to enter is respectfully requested.

There are two issues here: (1) the propriety of the SPE's reliance on § 1.97(e) to refuse to enter a declaration, and (2) the adequacy of applicant's compliance with § 1.116. (or, more accurately, § 1.195).

**The 1.197(e) Issue**

1. We know of no authority which says that a declaration can be refused entry because it cites a document which is not of record.

37 C.F.R. § 1.97(e) does not govern declarations. Rather, it relates to the certification which must appear in an information disclosure statement filed after final rejection, see 37 C.F.R. § 1.97(c)(1). The Declaration is not an IDS. Moreover, the newly cited references are primarily references supportive of patentability. As MPEP 2001.04, page

2000-3, col. 2 states, "the rules are not intended to require information favorable to patentability...." The duty of disclosure imposed by 37 C.F.R. § 1.56(b) relates to information which teaches against patentability.<sup>2</sup> There is no duty to disclose favorable references and, in any event, the Declaration was not characterized as an IDS and hence need not satisfy 37 C.F.R. §1.97(c) and (e).

The Appendix to this Petition sets forth exactly when and where each reference was made of record.

The references cited by the Declaration which were not previously made of record were:

- (1) Sanjeevi et al., 2002 (Table 1, item 8)
- (2) IOM 2002 (Table 1, item 9, and Table 2A, item 12)
- (3) Classen et al., 2001 (Table 1, item 10)

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<sup>2</sup> 37 CFR 1.56(b) defines materiality as follows:

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.  
[emphasis added]

- (4) Karvonen, et al. 2000 (Table 2A, item 2)
- (5) Yang, et al. 1998 (Table 2A, item 3)
- (6) Classen, et al., unpubl. (Table 2A, item 4)
- (7) DeStefano et al., 2001 (Table 2A, item 8)
- (8) Classen et al. reanalysis of Dahlquist
- (9) Classen et al., Medical Hypotheses 2001 (¶12)
- (10) M-M-R III vaccine PPI

References (1), (3), (6), (8) and (10) were plainly cited to support patentability, and consequently there was no §1.56 duty to disclose them. Thus, references (1), (3), (6), (8) and (10) above cannot be refused consideration merely because no certification was made under 37 C.F.R. § 1.97(e).

With regard to references (2) and (5), these references were disclosed to the PTO on October 18, 2002, and the persons having the duty of disclosure did not become aware of them until after July 18. Hence, Applicant could have made the certification under § 1.97(e) at the time of disclosure, and does so now, *nunc pro nunc*. See enclosed IDS listing (2) and (5) above.

While Applicant was aware of reference (4) in 2000, the diabetes paper does not address vaccines and so Applicant did not believe there was a duty to disclose it. It is mentioned in the Declaration because Counsel, in attempting to find a published account of the LaPorte data alluded by PIDJ, found it in a post-July 18 MEDLINE search. Moreover, it is cited in the Declaration merely to rebut PIDJ's inference from LaPorte's work, i.e., that the apparent increase in diabetes incidence was a surveillance effect. Hence, it arguably should be considered as a reference cited in favor of patentability, and considered on that basis.

Finally, (7) is a follow-up study to DeStefano (ref. DE) and while (7)'s conclusions are similar to those of ref. DU (hence cumulative in that regard), it is cited because it contains data (a timing-based difference in relative risk) which supports Applicant. So we believe that (7), too, should be considered on that basis.

It follows that § 1.97(e) is not a proper basis to refuse to consider any of the references cited in the Declaration, let alone the Declaration itself. However, if a reference thus cited is not of record, then at most it is grounds to disregard that reference, and the discussion thereof, not to ignore the entire Declaration. Indeed, a declarant may make statements about the state of the art without actually citing any art.

**The § 1.116 / § 1.195 Issue**

The Examiner also cites 37 CFR 1.116. Rule 1.116 governs the consideration of amendments after final rejection. It permits amendments which fall in one or more of the following categories:

- (1) they cancel claims;
- (2) they comply with an express PTO requirement of form;
- (3) they present rejected claims in better form for consideration on appeal; or
- (4) they touch the merits of the application, and a showing is made of "good and sufficient reasons why they are necessary and not earlier presented".

The amendment filed October 18, 2002 was entered, presumably on the basis of (1)-(3) above.

Formally speaking, 37 CFR §1.116 applies to amendments, not declarations or exhibits. With regard to the Classen declaration and exhibits, we assume that the Examiner intended to rely on 37 CFR 1.195, which reads as follows:

Affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reasons why they were not earlier presented.

Note that in contrast to 1.116(b), there is no requirement of a showing of necessity. Hence, we need only consider the reasons why the declaration and exhibits were not earlier presented.

Plainly, any reference published after the final rejection was mailed (November 5, 2001) could not have been presented prior to that action. This "safe haven" would embrace:

Table 1, item 7, Classen et al. (2002), especially since it is really a courtesy copy of a previously submitted manuscript, which was (mis)construed by the final rejection;

Table 1, item 8, Sanjeevi et al. (2002); and

Table 2A, item 12, the IOM Study (Mar. 2002).

It follows that there are good and sufficient reasons to enter the Declaration so that at least its comments on these new references may be considered.

Besides discussing these new references, the Declaration also addresses certain art of record, as well as the new exhibits

Table 1, item 10, Classon and Classon (2001);

Table 2A, item 8, DeStefano (2001);

Table 2A, item 9, Classen et al.(2001)'s unpublished reanalysis of ref. HK; Classen et al., Medical Hypothesis article; and

the M-M-R II vaccine physician's package insert.

It was only when Counsel began drafting the second Appellant's Brief that it became apparent that there were several references which the Examiner had nominally relied upon but which had not been specifically analyzed by the office action. Because the Examiner had not applied them in a clear and specific manner, these references had not been specifically addressed in the body of any amendment. This meant that, if the case were to go up on appeal, it could easily find itself remanded for proper consideration of those references.

To a large extent, these references were already addressed in the "Scientific Evidence" exhibits made of record on December 19, 2000. Indeed, the IDS of February 1, 2001 was based on those exhibits. However, Counsel was concerned that these exhibits, not being attached to a Declaration, might not be given the weight they deserved. In addition, Classen had certain unpublished data reanalyses which expanded on the points made in these exhibits.

The Declaration thus formalized and expanded upon the points made in the "Scientific Evidence" exhibits, and in doing so, it was supported by the aforementioned items.

37 C.F.R. § 1.116 and § 1.195 are intended to strike a balance between the PTO needs to reach closure in prosecution and to find out the truth concerning patentability. Here, the equities warrant granting the request/petition and entering the Declaration and Exhibits.

If the SPE or the Group Director holds that certain Exhibits should not be considered, then the Declaration should still be entered, and the Examiner simply instructed to ignore those portions of the Declaration which address the problem exhibits. The baby should not be thrown out with the bath water.

Conditional Petition Under 37 CFR \$1.183

If the petition under 37 CFR \$1.181 is denied in whole or in part, Applicant petitions under 37 CFR 1.183 that the applicable rules be waived to permit entry of the declaration and exhibits. Please charge the petition fee to deposit account 02-4035.

37 CFR 1.183 provides

In an extraordinary situation, when justice requires, any requirement of the regulations in this part which is not a requirement of the statutes may be suspended or waived by the Commissioner or the Commissioner's designee, sua sponte, or on petition of the interested party, subject to such other requirements as may be imposed. Any petition under this section must be accompanied by the petition fee set forth in \$1.17(h).

The statute does not require refusal of entry of declarations or exhibits after final rejection and hence is not a barrier to relief under \$1.183.

We believe that this is an "extraordinary situation", in which "justice requires" relief.

First of all, the Examiner's rejection is inconsistent with the PTO's treatment of three counterpart applications that have issued as patents:

5,728,385

5,723,283

USSN - 08/591,651

6,420,139

Not only did the PTO, in all three cases, consider the claims to be enabling, all of the references relied on by the Examiner in connection with the instant enablement rejection were of record during the prosecution of the '139 patent.

Secondly, Applicant cannot, by normal PTO procedures, force consideration of the declaration and exhibits without substantial loss of patent term.

The present application is a pre-GATT case, hence ineligible for RCE practice. Since its effective filing date is in 1994, it is ineligible for the transitional §1.129 practice, too. Filing a continuation would result in loss of pre-GATT status, resulting in a patent term expiring in 2013 (the priority application having been filed in 1993).

USSN - 08/591,651

In contrast, if this case were allowed, and Applicants cancelled the claims rejected for double patenting,<sup>3</sup> and the patent issued in 2003, the patent would expire in 2020.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant(s)

By

  
Iver P. Cooper  
Registration No. 28,005

Enclosure

-Appendix  
-IDS

624 Ninth Street, NW  
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Telephone No.: (202) 628-5197  
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IPC:ma:lms  
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<sup>3</sup> There was a double patenting rejection of method claims 6, 32-33, 56-57, 101, 103, 128-148, 156, 157 and 160 over the '395 and 283 patents. Claims 156 and 157 were cancelled by substitute amendment "A" filed June 21, 2002. Claim 160 was cancelled by the October 18, 2002 amendment. Applicants would immediately cancel the method claims if the Examiner agreed to allow the kit claims.

There is no double patenting rejection of record over the '139 patent, which issued July 16, 2002 on a later-filed application. Its claims are to methods, not kits. If the Examiner wishes to make such a rejection, she must withdraw finality, in which case the declaration and exhibits must be entered as a matter of right.

**Appendix**

Table 1 (references supportive of applicant)

1: cites spec and Classen et al. (1997); latter was Ref. GQ considered by Examiner on February 16, 2001.

2: same as above.

3: just cites spec.

4: cites spec and Classen et al. (1999); latter was Ref. GO. Also distinguishes Blom et al. (1991), ref. AS.

5: cites Classen et al. (1997), ref. GQ. Also Blom et al. (1991), discussed below.

6: cites Classen et al. (1997), ref. GQ; Classen et al. (1996), ref. DQ. Distinguishes Willis et al. 1997 (see discussion of Table 2B, item 7, below) and Petousis-Harris (ref. HE). Also cites Scott et al. 1992 (ref. FV) and Gunn et al. 1989 (ref. IS) on minor point.

7: cites Classen et al. (2002), a recent publication of text previously submitted to the PTO as a draft manuscript on August 17, 2001. Also cites Classen et al. (1999), ref. HR. Distinguishes Karvonen et al. 1999 (ref. EV) and Jefferson et al. (ref. HP).

8: cites newly discovered reference Sanjeevi et al. (2002) in support of patentability.

9: cites newly discovered reference IOM (March 2002) in support of patentability. But see Table 2A, item 12.

10: cites Classen and Classen (2001), a new reference, solely in support of patentability. This is at least partly duplicative of the disclosure on pp. 37-40 of the "Scientific Evidence" paper, of record.

Table 2A

1: cites Moulton, but only insofar as it is discussed in

PIDJ, made of record by the Examiner.

2: cites LaPorte as discussed by PIDJ. Speculates that cited data was that published in Karvonen, et al. (2000), which as discovered in a post-July 18, 2002 MEDLINE search by Counsel.

3: cites LaPorte again. Refers to post-July 18, 2002 MEDLINE search by Counsel which identified Yang et al. 1998.

4: cites parent, et al. 1997, ref. FL, and a new, unpublished manuscript by Classen. The latter supports patentability and hence is not subject to 1.97.

5: cites Blom, et al. 1991, ref. AS.

6: cites Graves et al., ref. EF.

7: cites Eurodiab, ref. EB.

8: cites DeStefano et al. (1997) ref. DU. Also refers to a follow-up study, DeStefano et al. (2001). The latter, to the extent against patentability, is cumulative with DU. It is cited for one point on which it supports patentability and hence not subject to 1.97.

9: cites Dahlquist et al. (1995), ref. HK, and Classen et al. (1996)'s unpublished reanalysis.

10: cites Heijbel, et al. 1997, ref. EI.

11: cites Elliot, et al., ref. IJ. Cohort data appears in a cited Classen document "Scientific Evidence...", made of record on December 19, 2000.

12: cites IOM study (March, 2002), newly discovered.

Table 2B

1: PIDJ was made of record by the Examiner.

2: Hiltunen is ref. EL. The cited Classen (1996) and (1997) articles are of record, refs. DQ and GQ.

3: Karvonen is ref. EV.

USSN - 08/591,651

4: Bedford is ref. HD.

5: Jefferson #1 is ref. HP.

6: Jefferson #2 is ref. EQ.

7: Willis is cited in PIDJ. IT is further discussed on page 50 of the "Scientific Evidence" monograph made of record on December 19, 2000.

8: Petousis-Harris is ref. HE.

9: CDC is ref. IN.

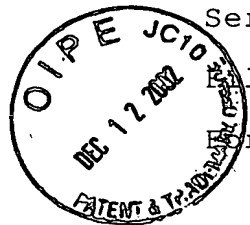
Miscellaneous

12: cites Classen, et al., Medical Hypotheses article (2001).

13. M-M-R II vaccine Physician Package Insert.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ) Art Unit: 1643  
)  
CLASSEN, John B. ) Examiner: B. BRUMBACK  
)  
Serial No.: 08/591,651 ) Washington, D.C.  
)  
Filed: February 12, 1996 ) December 12, 2002  
)  
For: METHOD AND COMPOSITION FOR ) Docket No.: CLASSEN=1A  
AN EARLY VACCINE... )



THIRD INFORMATION DISCLOSURE STATEMENT [IDS]

Honorable Commissioner of Patents  
Washington, D.C. 20231

S i r :

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed:

[ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above-identified international application. See 37 CFR 1.97(b).

[ ] B. before the mailing date of a first office action on the merits. See 37 CFR 1.97(b).

[ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary certification (box "i" below) or paid the necessary fee (box "ii" below). See 37 CFR 1.97(c).

[ ] i. Counsel certifies that, upon information and belief, each item of information listed herein was either (a) cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS or (b) was not cited in a communication from a foreign

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patent office in a counterpart foreign application and was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

- [ ] ii. Credit Card Payment Form, PTO-2038, authorizing payment for the fee set forth in 1.17(p), presently believed to be \$180, is attached.

[X] D. after (A), (B) and (C) above, but before payment of the issue fee. Applicant petitions under 37 C.F.R. 1.97(d) for consideration of this IDS. Credit Card Payment Form, PTO-2038, authorizing payment for the fee set forth in 1.17(i)(1), presently believed to be \$130 is attached. Counsel certifies that, upon information and belief, each item of information listed herein was either (i) cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS or (ii) was not cited in a communication from a foreign patent office in a counterpart foreign application and was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

[ ] E. As a submission in accordance with the transitional procedure for limited examination after final rejection pursuant to 37 CFR §1.129(a). Pursuant to MPEP §706.07(g), page 700-66, col. 2 (August 2001), this IDS is treated as if filed with a period set forth in 37 CFR §1.97(b) and considered without the petition and petition fee required by 1.97(d).

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO-1449) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document is attached, except as explained below.

[ ] While an IDS filed under §1.97 must contain a "list of all patents, publications or other information submitted for consideration by the Office", see §1.98(a) (1), the only requirement for the list is that it provide the information set

forth in §1.98(b). There is no requirement that a form PTO-1449 be used (MPEP §609 merely says that use of this form is "encouraged"). Counsel has used a list provided to him by Applicants, and not transferred the information to a PTO-1449, to avoid the risk of any inadvertent error in transferring the information.

[ ] A. Documents \_\_\_\_\_ are deemed substantially cumulative to documents \_\_\_\_\_, and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] B. Certain documents were previously cited by or submitted to the Office in the following prior application(s), which are relied upon under 35 U.S.C. 120:

[insert serial number/filing date]

Applicants identify these documents by attaching hereto copies of the form PTO-892s and PTO-1449s from the files of the prior applications or a fresh PTO-1449 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application. If copies of any of these documents cannot be found in the files of the prior applications, the Examiner is requested to so notify counsel before taking action in this case, so replacement copies can be submitted. While an IDS filed under §1.97 must contain a "list of all patents, publications or other information submitted for consideration by the Office", see §1.98(a) (1), the only requirement for the list is that it provide the information set forth in §1.98(b). There is no requirement that a form PTO-1449 be used (MPEP §609 merely says that use of this form is "encouraged") and no prohibition on submitting a copy of a form PTO-1449 or form PTO-892 from a prior case. Indeed, the re-use of such forms is desirable as it avoids error in transferring the information, and evidences that the reference was considered in a prior application. A previously accepted PTO-1449, or an examiner-prepared PTO-892, necessarily complies with §1.98(b).

[ ] 3. Documents \_\_\_\_\_ are not in the English

language. In accordance with 1.98(a)(3), Applicants state:

- [ ] documents \_\_\_\_\_ already contain an English language abstract, summary or claim set.
- [ ] a publicly available abstract is attached to each of documents \_\_\_\_\_, and the source of each abstract is indicated thereon.
- [ ] documents \_\_\_\_\_ are patents or published patent applications for which counterpart English language patents or patent applications exist, and are enclosed, as follows:

<u>Foreign Lang. Doc.#</u>	<u>English Lang. Doc.#</u>
----------------------------	----------------------------

[insert]

[insert]

- [ ] applicants have prepared an English translation of at least the pertinent portions of documents \_\_\_\_\_, and copies are attached.
- [ ] A concise explanation of the relevance of documents \_\_\_\_\_ is found in the attached search report from the \_\_\_\_\_ Patent Office (see reply to Comment 68 in the preamble to the final rules; 1135 OG 13 at 20).
- [ ] A concise explanation of the relevance of documents \_\_\_\_\_ is set forth as follows:

[Insert concise explanation of relevance]

4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 and 68 in the preamble to the final rules; 1135 OG 13 at 20).

5. If the month of publication of a nonpatent reference is not stated, it is because it is not apparent from review of the reference. If requested to do so by the Examiner, Applicants will attempt to locate and write to the publisher.

If the publication date of a cited document is set forth only as a publication year, and that year is prior to the year of filing or, if priority is claimed, year of priority of this application, then the particular month of publication is not in issue. Likewise if that publication year is after the year of filing of this application, the month of publication is not in

issue.

If the date of publication of a nonpatent reference is stated, then, except as explained below, it is the nominal date stated in the reference, or in a larger document (journal or book) from which the reference was extracted. Applicants reserve the right to challenge this date by contacting the publisher to determine the actual shipment date, or by contacting recipients to determine the receipt dates.

6. Other information being provided for the examiner's consideration follows:

**Copies of references KB-KC were previously submitted on October 18, 2002, as exhibits to the Classen Declaration.**

7. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless otherwise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

8. The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this paper or credit any overpayment to Deposit Account No. 02-4035.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant

By: \_\_\_\_\_

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**FORM PTO-1449**

**U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE**

ATTY DOCKET NO: CLASSEN=1A

**SERIAL NO: 08/591,651**

**LIST OF DOCUMENTS CITED BY APPLICANT**  
(Use several sheets if necessary)

**APPLICANT: CLASSEN, John B.**

**FILING DATE:** February 12, 1996

**GROUP: 1643**

**U.S. PATENT DOCUMENTS** (include at least patentee, patent number and issue date)

[illegible]

**FOREIGN PATENT DOCUMENTS** (include at least document number, publication date and country)

[illegible]

**OTHER DOCUMENTS** (include author, title, name of publication, volume, pages & date of publication)

[illegible]

**EXAMINER**

**DATE CONSIDERED**

**EXAMINER:** Initial if reference considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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child health clinic since, in each instance, non-attenders were less likely than expected to have the problem. This was particularly true for feeding and sleeping problems as a baby, as well as at age 5. It was apparent for children who had cried frequently as a baby, those described as irritable, tearful or having one of the hyperactive symptoms at 5, and children with a history of stomach aches, sore throats and mouth breathing.

Children who had *never* visited a dentist presented with a quite different set of problems. They were more likely to have many of the behaviour attributes associated with the difficult or hyperactive child. They also included more children than expected who were described as fussy, over-particular, or solitary. They were less likely than expected to have a history of eczema, hay fever or to suck their thumbs.

Children who never attended a child health clinic or a dentist were less likely to be suspected of having hearing difficulty. Whether this means that fewer children with hearing loss were included in these groups, or alternatively that the index of suspicion was lower and the children with hearing loss were less likely to have been identified, is one which we shall examine when analysing data from the audiograms in the 10-year follow-up.

### Conclusions

1. Health visitor home visits in the first 6 months of life were significantly less likely to occur: (a) if both parents were Asian; (b) if the child had an unsupported single parent, or neither natural parent; (c) if the child had moved house; and (d) if the child was resident in London and the South East of England.
2. Children were less likely to have ever attended a child health clinic if their mother smoked heavily, they were residents in a rural area or in Scotland, the East Midlands or East Anglia.
3. Children never seen at a child health clinic were significantly less likely to have behaviour, sleeping or feeding problems, intermittent stomach aches, sore throats or mouth breathing.
4. Low birthweight children were more likely to be seen at a birth follow-up clinic.
5. Children seen at birth follow-up clinics were more likely to have a variety of sensory, respiratory and behaviour problems.
6. Failure to visit a dentist was more likely if: (a) the child was in the manual social classes; (b) the mother was a single parent; (c) the child had three or more siblings; (d) the household had moved three or more times; (e) the child lived in a poor urban area; or (f) the child resided in East Anglia or the Midlands.

## CLASSEN I E

N.R. Butler and Jean Golding, eds.  
From Birth to Five: A Study of the  
Health and Behaviour of Britain's Five Year  
Olds  
CHAPTER 20 (Pergamon Press  
1986)

## Immunisations

by JEAN GOLDING

### Introduction

Even with the advanced technology of the 1980s there is still no known cure for many of the major infections of childhood, although treatment may ameliorate the diseases. As has been recognised since the eighteenth century, the most effective method of preventing major epidemics of infection is by means of inoculation or vaccination. This process results in antibodies to the particular disease being created in the patient without their having to undergo the disease itself. It is true that in some cases a very mild form of the illness will result from the vaccination, but until recently this has been considered a very small price to pay for immunity from the disease.

Information on immunisations was not collected on the children involved in the 1946 cohort. The 1958 study, however, enquired as to whether the children had been immunised against diphtheria, polio and smallpox. Analysis of the data collected when the children were 7 (Davie, Butler and Goldstein, 1972) showed that three-quarters of the children had been vaccinated against smallpox, 95% had had at least one immunisation against polio and 94% had been given some protection against diphtheria. For each type, children in the upper social classes were more likely, and those in social classes IV and V were least likely, to be immunised. There were regional differences, with Scotland having higher than average immunisation rates and the North of England having the lowest rates.

### The Present Study

Health visitors asked the mothers for details of all immunisations given to the study child up to the time of interview. As shown in Table 20.1, over half the children had had at least some of their immunisations at a child health clinic, and 40% were immunised only at a general practitioner surgery.

Table 20.2 shows that the proportion of children immunised against

TABLE 20.1 Places where the children had received their immunisation

Place* where immunisation(s) given	Number of children
GP surgery	4446 (39.8%)
Child health clinic	5279 (47.2%)
GP surgery and child health clinic	1355 (12.2%)
Elsewhere only	87 (0.8%)
All known	11,167 (100.0%)

\*Categories mutually exclusive.

TABLE 20.2 Immunisations received by the 12,692 children for whom immunisation histories were recorded

Immunisation	Number of children
Diphtheria	12,239 (96.4%)
1 or more	11,793 (92.9%)
2 or more	11,373 (89.6%)
3 or more	5322 (41.9%)
4 or more	
Tetanus	12,253 (96.5%)
1 or more	11,797 (92.9%)
2 or more	11,377 (89.7%)
3 or more	5345 (42.1%)
4 or more	
Pertussis	11,851 (93.4%)
1 or more	11,364 (89.5%)
2 or more	10,878 (85.7%)
3 or more	1339 (10.5%)
4 or more	
Polio	12,100 (95.3%)
1 or more	11,646 (91.8%)
2 or more	11,195 (88.2%)
3 or more	5101 (40.2%)
4 or more	
Measles immunisation	7440 (58.6%)
Smallpox immunisation	2747 (21.6%)
BCG	868 (6.8%)
No immunisations at all	317 (2.5%)

diphtheria and polio was almost identical to that found in the 1958 cohort. Altogether 88% of the study children had had at least three immunisations against each of diphtheria, tetanus, pertussis (whooping cough) and polio. The proportion vaccinated against smallpox had dropped from three-quarters to one-fifth, but this was still higher than expected, since in the early 1970s smallpox had been almost eliminated from the world population.

The epidemiological features of diphtheria, tetanus, pertussis and polio immunisation were, at this time, almost identical to one another. We shall, therefore, describe the associations of only one, and have chosen pertussis because of its topicality. In addition, we shall discuss the features associated with measles immunisation and BCG.

### Pertussis Immunisation

Pertussis vaccine is normally given in combination with diphtheria and tetanus vaccines, but any adverse reactions appear to be associated with the pertussis part of this combination. That relatively minor reactions are common was clearly demonstrated in a study by Barkin and Picchero (1979). They studied all children receiving a combined vaccine for diphtheria, tetanus and pertussis (DTP) in their practice, during an 8-month period in 1977-8. Questionnaires were filled in 48 hours after the immunisation of 1232 children. During the 2 days, 49% had had a temperature between 100°-102°F and a further 4% had had a temperature of over 102°F. Only 18% of the sample had reported no behaviour change after the immunisation, 34% had been reported as irritable, 35% as crying more than normally, and 13% as screaming. Other problems which were reported by the parents included listlessness, decreased appetite and vomiting. There were no reports, of convulsions.

Several studies have now taken place in an attempt to assess whether pertussis vaccination does result in an increased incidence of convulsions with an encephalopathy. Stephenson (1980) studied the EEG results of twelve children who had had febrile convulsions after receiving pertussis vaccine, and compared these with three children who had had convulsions during an episode of whooping cough itself. He contrasted his results with those from 630 children who had had febrile convulsions, not associated with pertussis or its vaccine. He found that children with febrile convulsions after the vaccine had EEGs that were similar to the children whose convulsions were classified as 'anoxic' (i.e. 'more like fainting fits'); the three children who had had convulsions with their episode of whooping cough had EEGs that were more consistent with a diagnosis of encephalopathy.

In a publication from the Department of Health and Social Security

(1981) three studies were reported. Dudgeon and his colleagues examined fifty apparently well-documented cases of adverse reactions to pertussis vaccine, and showed that thirty-four could possibly be related to the immunisation itself: thirteen of these children had chronic epilepsy; thirteen had an acute encephalopathy; and eight had infantile spasms. This study is difficult to interpret, as the authors recognise, because of lack of comparison with a control population.

The second study was made by Meade and his colleagues who examined records of 229 infants identified either from the archives of the Association of Parents of Vaccine Damaged Children or from notifications to the Committee on Safety of Medicines. They commented that the data were largely unsatisfactory for epidemiological analysis, but nevertheless concluded that the evidence as a whole left little doubt that pertussis vaccine was associated with an increased incidence of convulsions, but that evidence for brain damage was inconclusive.

A different approach again was involved in the National Childhood Encephalopathy Study. This involved 1000 children admitted to hospital with an acute neurological illness in the age group 2-36 months. Two controls were chosen for each case, matched for age and area of residence. Immunisation histories were compared between cases and controls. Significantly more of the index cases (3.5%) had had pertussis vaccine within 7 days of the onset of the illness compared with 1.7% of controls. This gave a relative risk of encephalopathy associated with vaccination of 2.4, significant at the 0.001 level. Of the thirty-five pertussis vaccine associated cases, thirty-two were regarded as neurologically normal before the illness; twenty-one of these recovered completely.

The conclusions of the report were that a link might well exist between pertussis immunisation and neurological illness. The authors emphasise that in many instances where adverse reactions had been noted the immunisation had been given in the presence of contraindications. But this assumes that we know which factors to avoid. Illingworth (1980) reported a strange conglomeration of factors which mothers had stated were the reason for their child not having been immunised against whooping cough. These included: the child had been given oxygen at birth; was pre-term; had had jaundice; was a breech; was a twin; had had nappy rash. In America the OCIP recommendations are largely concerned with any severe side effect noted after a preceding dose. They state that the presence of an evolving neurologic disorder contraindicates the use of pertussis vaccine, but that a static neurologic condition, like cerebral palsy, or a family history of neurologic disease is not a contraindication (MMWR, 1981). Valman (1980b) stated that family or personal history of allergy is not a contraindication to pertussis immunisation, but Anand (1980) reported that, according to the drug

firm Wellcome, a history of severe allergy should be a contraindication to the use of the vaccine.

It is salutary to compare the adverse effects of the vaccine with those of the disease. McKendrick, Gully and Geddes (1980) studied abnormalities in children with pertussis admitted to hospital 1978-9. As many as 40% of these children had pneumonia, 13% had cyanotic and apnoeic attacks and 7% had convulsions. They found no difference in the rate of complications among children who were under 6 months of age compared with those who were older. A further interesting study on whooping cough was carried out in Cardiff by Vesselinova-Jenkins and her colleagues (1978). She, too, found that 7% of the children had convulsions, but was also able to analyse the data according to whether the child had had any vaccinations prior to the whooping cough episode. She found that among 101 children who had had whooping cough subsequent to a completed course of immunisations, only one had a convulsion; among twelve children who had inadequate vaccination one child had convulsions with the episode of whooping cough; but among 116 children who had no pertussis immunisation at all, as many as fourteen had convulsions.

An attempt has been made by Koplan and his colleagues (1979) to contrast the benefits and costs of programmes of pertussis vaccination in America. On the basis of information available to them at that time, they predicted that if immunisation were to cease, there would be a 71-fold increase in cases of whooping cough with an almost four-fold increase in deaths from whooping cough, as well as 3.2 cases of encephalitis associated with the disease. With a vaccination programme they predicted 0.1 cases of encephalitis associated with whooping cough and five cases of post-vaccination encephalitis per 1,000,000 children. They concluded that a vaccination programme would reduce by 61% the costs related to pertussis. Such an analysis is still awaited in the British scene.

In this section we shall examine those factors associated with children who either had never been immunised, or who had been immunised, but not for pertussis. As we have already noted, there is considerable anxiety concerning possible adverse effects of pertussis immunisation. It is, therefore, pertinent to examine the data relating to the children who were not immunised at a point in time prior to the adverse propaganda with the consequent drop in uptake.

There were no differences between the sexes in the uptake of pertussis immunisation, nor were low birthweight infants more, or less, likely to receive such an immunisation. There were differences, however, with the type of feed the child had had as a baby (Fig. 20.1). Children who had never been breast fed were twice as likely never to have been immunised at all.

Uptake of immunisations varies with various characteristics of the

families. As shown in Fig. 20.1b, the older mothers were those who were less likely to have their children immunised at all—and less likely to have the child immunised against pertussis. This is closely linked to the fact that the children least likely to be immunised were those from the larger families.

As in the 1958 cohort, children in the non-manual social classes were the most likely to be immunised, and children in social class V were

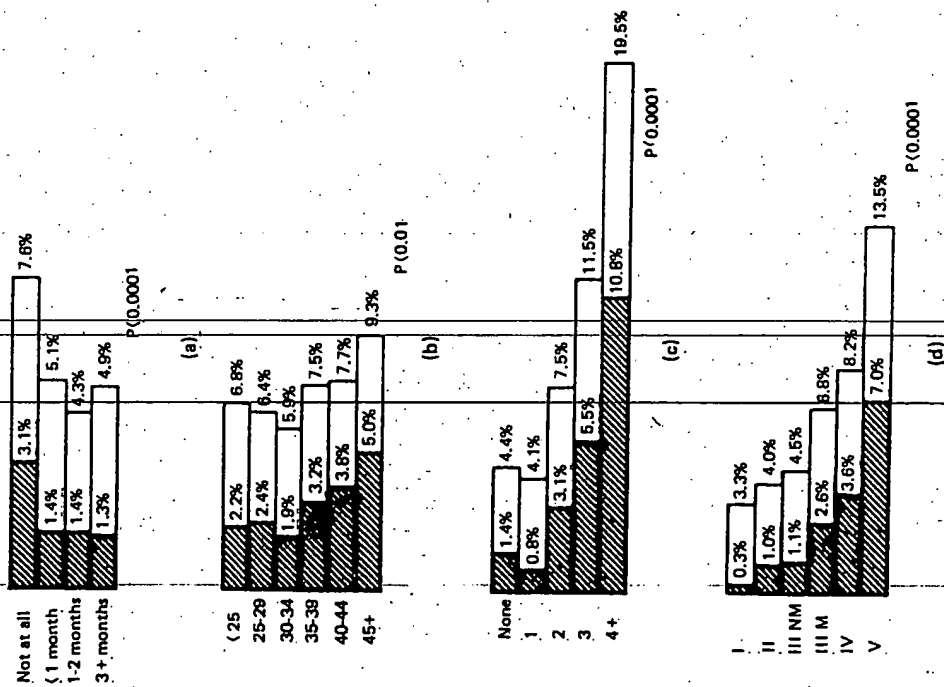


FIG. 20.1 Proportion of children not immunised against pertussis by (a) duration of breast feeding, (b) maternal age, (c) number of other children in the household, (d) social class

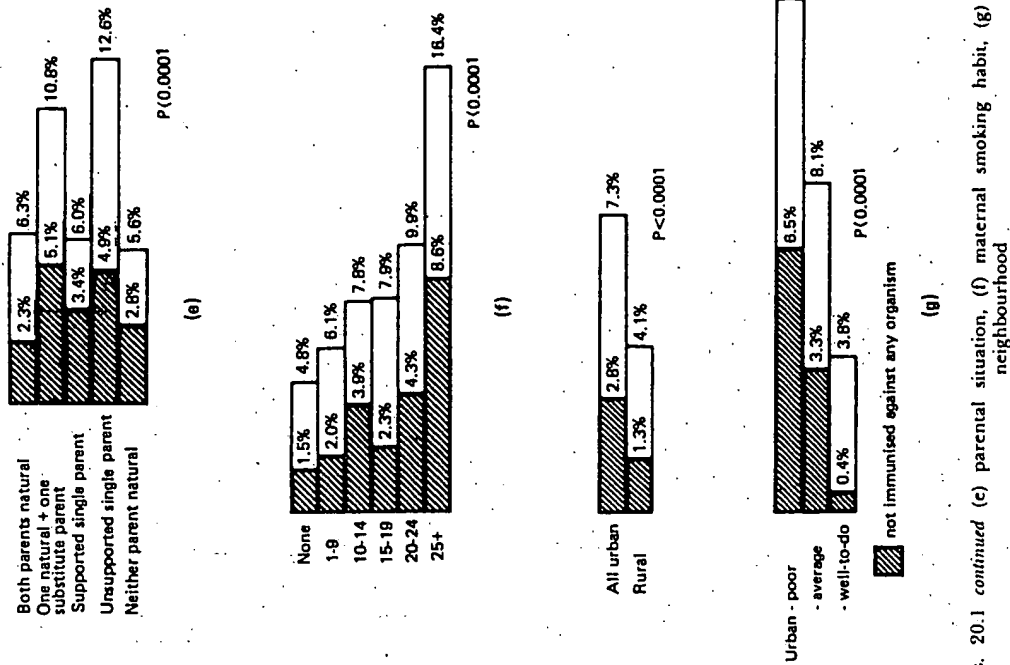


FIG. 20.1 continued (e) parental situation, (f) maternal smoking habit, (g) type of neighbourhood

most likely to be unprotected against pertussis (Fig. 20.1), or any of the other infections against which immunisations are available. A similar pattern was shown with parental situation. Children living with an unsupported single parent, and those with a step-parent, were more likely not to have been immunised.

As with so many of the factors we have examined, there was a strong association with the smoking habit of the mother (Fig. 20.1); the more

cigarettes she smoked; the less likely was the child to have been immunised.

Again, as shown for the 1958 cohort, there were significant regional differences (Fig. 20.2). Children living in Scotland were among the most likely to receive immunisations. Children who never received any form of immunisation were found proportionately more often in the northern counties of England and in Wales.

As we have shown in Chapter 19, children from rural areas are less likely to visit a child health clinic. Nevertheless, Fig. 20.1 demonstrates that residents of urban areas are more likely to fail to receive immunisations of any sort. In view of the distribution with social class, it is not surprising that there was a strong trend among the urban areas—compared with those in well-to-do areas, children in poor urban areas were at thirteen times the risk of never being immunised.

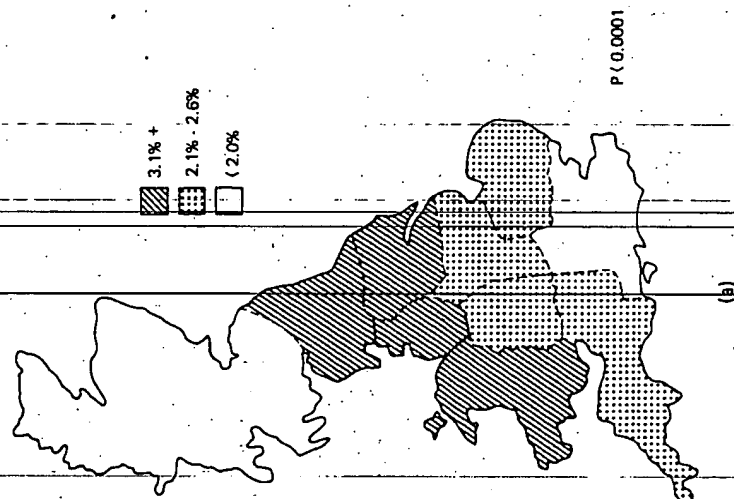


FIG. 20.2 Proportion of children in each region (a) not immunised at all

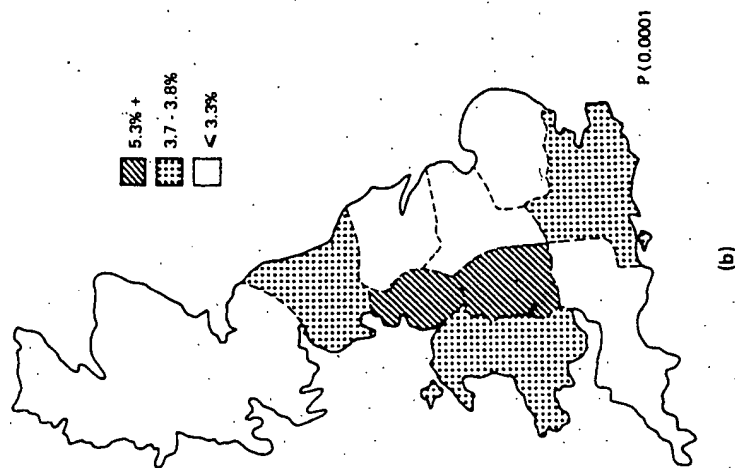


FIG. 20.2 continued (b) immunised but not against pertussis

Analysis of the inter-relationships of the eight factors described above demonstrated that four were of paramount importance in determining the failure of the child to receive pertussis immunisation. These were: the region of the country and type of neighbourhood in which the child lived; the number of other children in the family; and the number of cigarettes the mother smoked (Fig. 20.3). These accounted for the associations we had found with maternal age, social class, parental situation and the duration of breast feeding.

The characteristics of the children who were *never* immunised are shown in the left-hand columns of Table 20.3. As with children who had never been to a child health clinic, in many respects they had fewer problems than would have been expected from the population as a whole. There were, however, more children than expected with bronchitis and pneumonia, and more with hospital admissions. A third

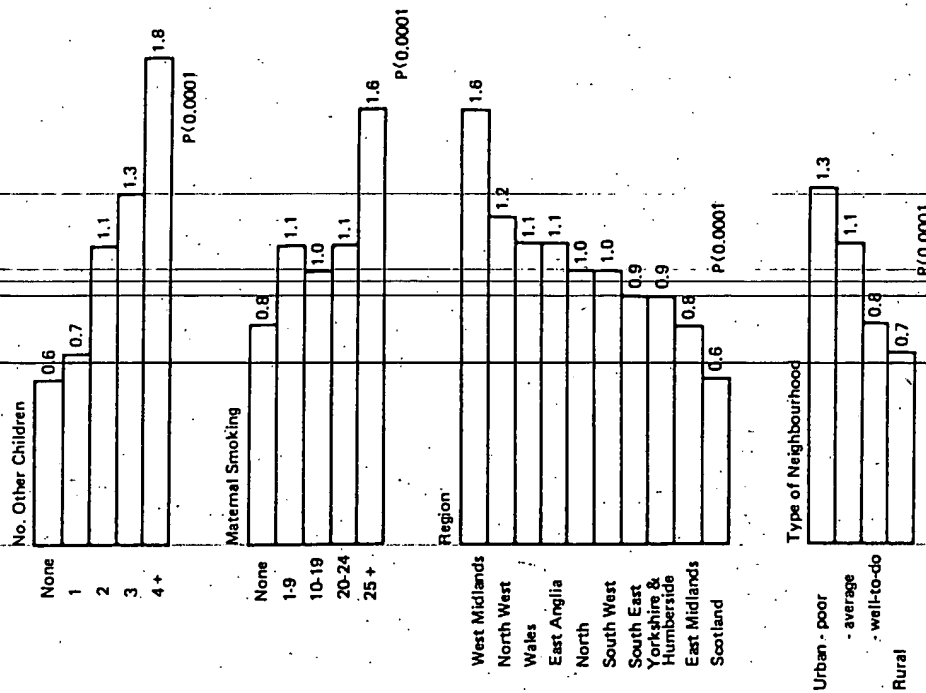


FIG. 20.3 Factors independently associated with failure to receive a pertussis immunisation (Relative Risk of not having the immunisation)

of the children who received no immunisations at all had never attended a child health clinic. This group were also less likely to have been taken to a dentist.

Among children who had been immunised, but not against pertussis, there were, again, more than expected who had been admitted to hospital. In addition, more children in this group had attended a birth follow-up clinic but were less likely to have been seen at home by a health visitor in the first months. The group contained an excess of accident

TABLE 20.3 The health and behaviour of children who either (a) were never immunised at all, or (b) were immunised but not against pertussis

Child's history	Never immunised Observed	R. Risk	Not pertussis Observed	R. Risk
Wets bed (1+ per week)	41	1.1	78	1.3*
Wets by day	34	1.0	48	0.9
Soils	16	1.2	16	0.7
Sleeping problems as a baby	29	0.7*	69	1.0
Sleeping problems at 5	65	0.8	120	0.9
Feeding problems as a baby	31	0.7	71	1.0
Feeding problems at 5	101	0.9	189	1.0
Temper tantrums (1+ per week)	69	1.5***	82	1.2
Destroys belongings	21	1.3	30	1.3
Fights other children	31	1.9***	25	1.0
Is irritable	66	1.5***	52	0.8
Takes things	13	1.7*	11	1.0
Is disobedient	53	1.5**	60	1.1
Tells lies	12	1.3	16	1.2
Bullies	20	3.2***	13	1.5
Is often worried	18	1.0	33	1.1
Is rather solitary	56	1.7***	56	1.1
Is miserable or tearful	18	1.8**	18	1.3
Is fearful or afraid	22	1.0	51	1.5**
Is fussy or over-particular	46	1.4*	48	1.0
Is very restless	110	1.1	173	1.1
Is squirmy or fidgety	47	1.2	65	1.1
Cannot settle	37	1.4*	45	1.2
Crying problem as a baby	31	0.7*	79	1.1
Not much liked	9	1.6	16	2.0**
Twitches/mannerisms	4	0.7	6	1.5
Bites nails	38	1.0	64	1.1
Sucks thumb	21	0.4***	82	1.0
Dysfluency	13	0.6	41	1.3
Other speech problem	45	1.3	76	1.4**
Headaches (1+ per month)	23	1.2	27	0.9
Stomach aches (1+ per month)	30	1.0	45	0.8
2+ Accidents	33	0.8	94	1.5***
Wheezing	81	1.2	149	1.4***
Eczema	20	0.6*	96	1.6***
Hay fever	8	0.6	23	1.1
Vision problem	7	0.6	22	1.2
Squint	24	1.0	47	1.2
Bronchitis	84	1.5***	112	1.3*
Pneumonia	11	1.9*	12	1.4
Repeated sore throats	42	0.7**	101	1.0

Continued

Table 20.3 continued

Child's history	FROM BIRTH TO FIVE	
	Never immunised Observed	R. Risk
Ear discharge	35	1.0
Mouth-breathing	66	1.0
Suspected hearing disorder	15	0.7
One hospital admission	76	1.3
2+ hospital admissions	36	1.5*
Tonsillectomy	6	0.9
Adenoidectomy	1	0.4
Circumcision	4	0.5
Hernia repair	4	0.8
Attended birth follow-up clinic	37	0.8
Not seen at home by HV < 6 months	24	1.1
Never been to child health clinic	110	3.8***
Never been to dentist	169	1.9****

(Relative Risks computed after standardisation for social class.)

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

repeaters, and more than expected had a history of wheezing or of eczema. These latter two associations could be interpreted in two ways: the lack of pertussis immunisation resulted in allergic diseases; or the presence of the allergic disorders was the reason for withholding the pertussis immunisation. The latter explanation seems the more likely.

Study of these two groups in more detail (Golding, in preparation) has shown that, in both, there was a comparatively high rate of hospital admissions for pertussis (whooping cough) itself. These episodes were frequently associated with bronchitis and pneumonia. Further analysis has shown that the children who had not been immunised against pertussis were more likely to be intellectually retarded by the age of 5. In many cases the retardation occurred in the children who had had the disease itself. As for convulsions associated with pertussis immunisation, we were able to identify four cases where this had occurred within 72 hours. This was twice as many as expected, but none of the four subsequently suffered from retardation or any other disability.

#### Measles Immunisation

The association of measles vaccine with severe adverse effects has received comparatively little attention in the literature. In America 1114

students were studied, a third having been given measles vaccine. Analysis of symptoms in the subsequent 21 days showed that the frequency of pyrexia was over twice as great in those who had been given the measles vaccine, compared with controls who had not been immunised (MMWR, 1981). In Hamburg Allerdist (1979) analysed eighteen cases where neurological complications had been reported after measles vaccine. Of these, four had had the immunisation less than 6 days prior to the convulsion and were assumed not to be associated with the vaccine; fourteen had had a convulsion between the 7th and 11th day from the immunisation date, and these he assumed to be causally related (this included two with an encephalopathy). He concluded from this data that the risk of febrile convulsions was 1 per 2500 immunisations, and the risk of slight encephalopathy was 1 per 17,650. Analysis of the National Childhood Encephalopathy Study also demonstrated an increased risk of encephalopathy between 7 and 14 days after measles immunisation; the risk was estimated at 1 in 87,000.

It is generally recognised that any harm that might result from the use of the vaccine is more than compensated for by the adverse associations of the disease itself. In the present study there were seven children with a fit 7-14 days after immunisation, but there was no evidence to suggest that this was associated with any long-term adverse effect. Balanced against this should be a least five children who had had convulsions in association with measles itself, one of whom was subsequently found to be severely retarded.

As already noted, over half the study children had been immunised against measles. The majority of these (5822 children) received the immunisation when they were 1 year of age. In this section we shall be describing the ways in which children who received the jab differed from the rest of the cohort.

As found with other health behaviour, there were no differences between the sexes. Children of low birthweight were no more, or less, likely to be immunised than the rest of the study group. There was again, however, an association with breast feeding—children who had been breast fed were more likely to have been immunised (Fig. 20.4).

There was a strong regional variation with South-west among those areas most likely to immunise against measles (Fig. 20.5). Children from Wales were significantly less likely to be immunised than those in England.

As with pertussis immunisation, children in rural areas were more likely to be immunised than those in urban areas (Fig. 20.4). In urban areas it was residents in the well-to-do suburbs that were most likely to have been protected in this way.

There was some evidence that the chance of the child being immunised against measles fell with the number of times the child had

## FROM BIRTH TO FIVE

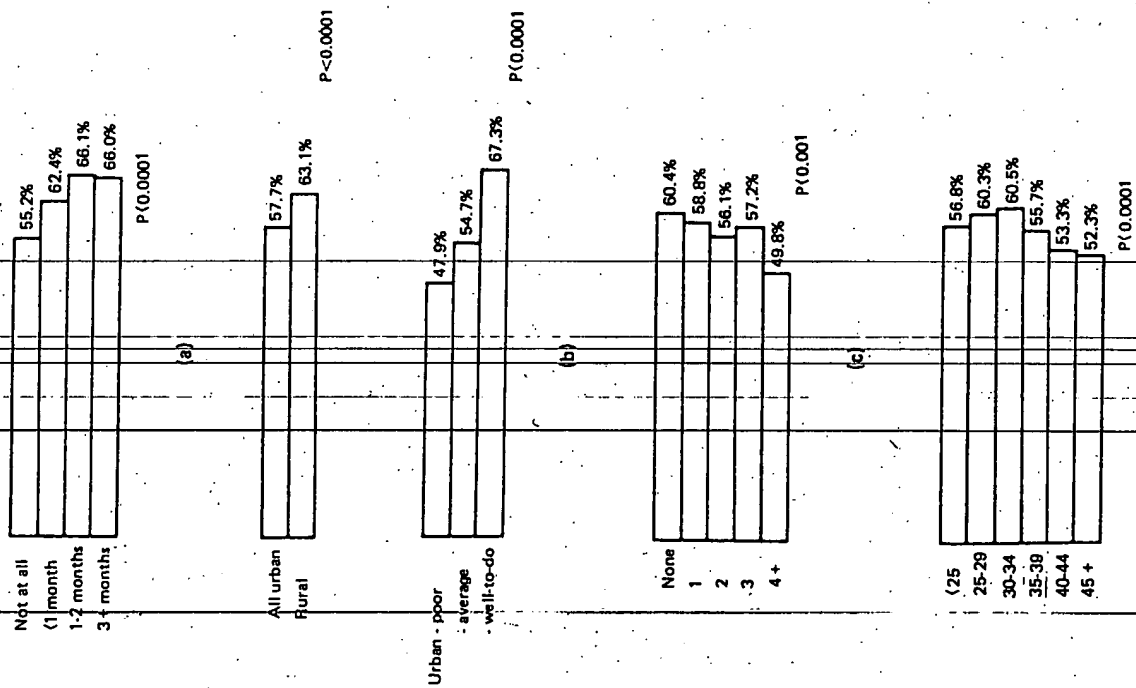


FIG. 20.4 Proportion of children immunised against measles by (a) duration of breast feeding, (b) type of neighbourhood, (c) number of household moves, (d) maternal age

## IMMUNISATIONS

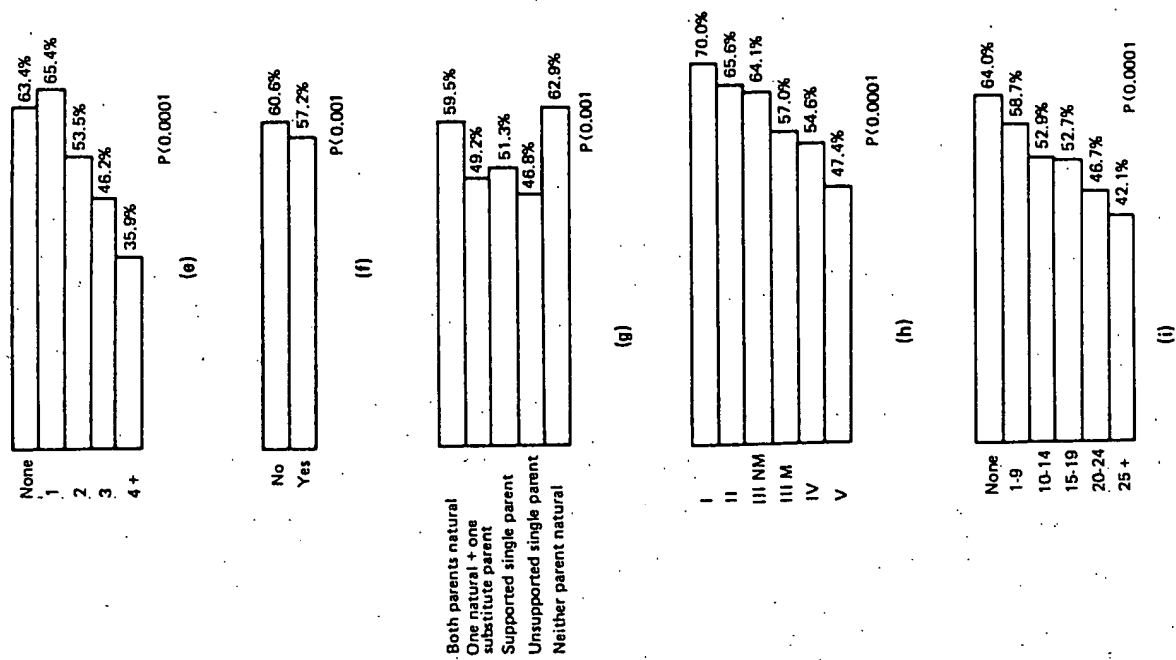


FIG. 20.4 (continued) (e) number of other children in the household, (f) whether mother employed during the child's life, (g) parental situation, (h) social class, (i) maternal smoking habit

moved house. Figure 20.4c shows, however, that the association is mainly among the frequent movers (at least four moves by the time the child was 5).

Other patterns are similar to those found with dental care. Mothers who were in their 40s, those with large families, those who had been employed, and those who were not living with the natural father of the child, were less likely to have had their child immunised against measles.

In addition, there were strong linear trends with social class (Fig. 20.4) and the number of cigarettes smoked by the mother. Thus, the more cigarettes she smoked, or the lower the social class, the less likely the child was to have been immunised against measles.

Indirect standardisation (Fig. 20.5) has shown that the uptake of measles immunisation is independently associated with: the region of

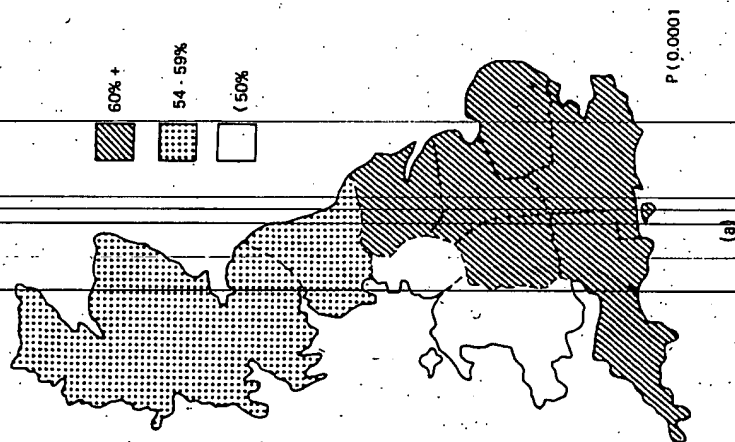


FIG. 20.5 Proportion of children in each region receiving (a) measles immunisation

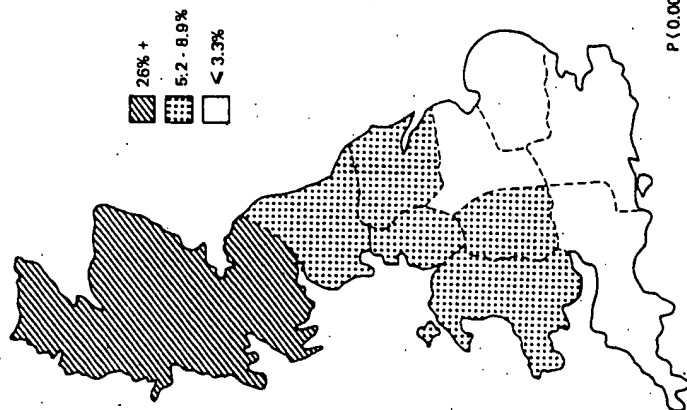


FIG. 20.5 continued (b) BCG

the country and the type of neighbourhood in which the child resides; the number of other children in the household; whether the household has moved frequently; and the maternal smoking habit. The other factors were no longer statistically significant once these five had been taken into account.

Children who had been immunised against measles showed no signs of adverse outcome (Table 20.4). Indeed, they were significantly less likely than expected to have been admitted to hospital on two or more occasions, and less likely to have had bronchiitis or pneumonia. Part of these differences may be explained by the contraindications to the vaccine, which include chronic diseases of the heart or lungs (Valman, 1980b). Other explanations include the increase in hospital admissions associated with measles in unimmunised children (nineteen cases) and

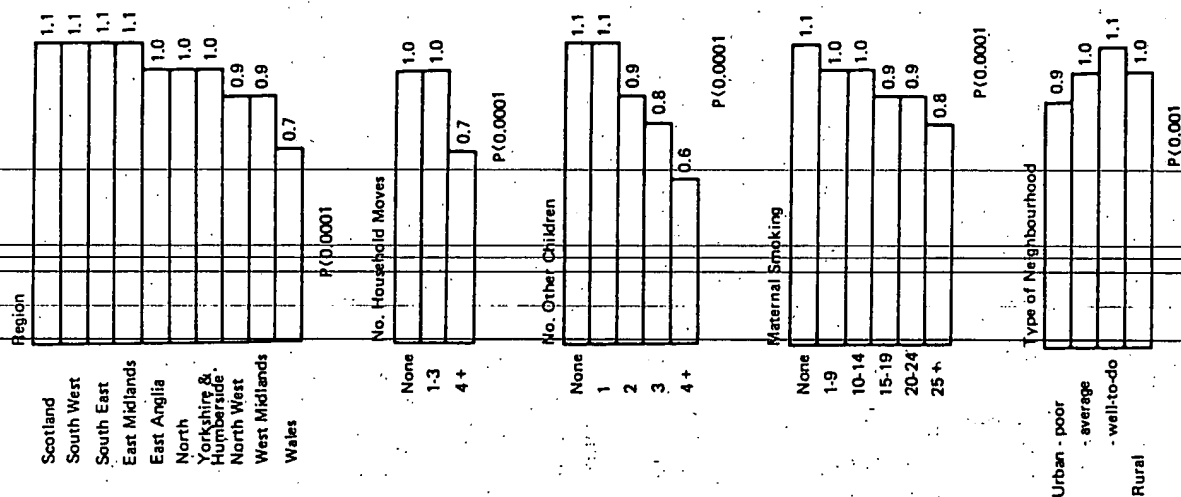


FIG. 20.6 Factors independently associated with uptake of measles immunisation (Relative Risks)

TABLE 20.4 The health and behaviour of children who were immunised against measles or given BCG

Child's history	Immunised against measles		BCG given	
	Observed	R. Risk	Observed	R. Risk
Wets bed (1+ per week)	709	0.9**	94	1.0
Wets by day	746	1.0	76	0.9
Soils	305	1.0	29	0.8
Sleeping problems as a baby	1029	1.0	119	1.0
Sleeping problems at 5	1850	1.0	200	0.9
Feeding problems as a baby	1002	1.0	120	1.1
Feeding problems at 5	2759	1.0	299	1.0
Temper tantrums (1+ per week)	782	0.9**	120	1.1
Destroys belongings	244	0.8**	33	0.9
Fights other children	236	0.8***	48	1.3
Is irritable	787	1.0	99	1.0
Takes things	108	0.8	17	1.0
Is disobedient	626	0.9*	83	1.0
Tells lies	123	0.8*	28	1.4
Bulies	86	0.8	18	1.4
Is often worried	415	1.0	43	0.9
Is rather solitary	624	1.0	91	1.1
Is miserable or tearful	179	1.0	11	0.5*
Is fearful or afraid	465	1.0	59	1.0
Is fussy or over-particular	647	1.0	82	1.0
Is very restless	2059	1.0	265	1.1
Is squirmy or fidgety	810	1.0	100	1.0
Cannot settle	465	1.0	65	1.1
Crying problem as a baby	1076	1.0	118	1.0
Not much liked	80	0.8	12	1.0
Twitches/mannerisms	54	1.0	8	1.2
Bites nails	840	1.0	105	1.1
Sucks thumb	1414	1.1***	119	0.8
Dysfluency	458	1.0	55	1.0
Other speech problem	755	1.0	74	0.8
Headaches (1+ per month)	414	1.0	54	1.1
Stomach aches (1+ per month)	729	1.1	77	1.0
2+ Accidents	863	1.0	125	1.2
Wheezing	1439	1.0	175	1.0
Eczema	868	1.0	102	1.0
Hay fever	327	1.0	36	1.0
Vision problem	242	1.0	24	0.8
Squint	515	0.9	57	0.9
Bronchitis	1112	0.9**	127	0.9
Pneumonia	83	0.7**	11	0.8
Repeated sore throats	1469	1.0	195	1.1
Ear discharge	803	1.0	73	0.8*

Continued

Table 20.4 continued

Child's history	FROM BIRTH TO FIVE		measles R. Risk	BCG given Observed	R. Risk
	Immunised Observed				
Mouth breathing	1395		1.0	167	1.0
Suspected hearing disorder	622		1.0	60	0.9
One hospital admission	1285		0.9*	183	1.1
2+ hospital admissions	437		0.9***	69	1.1
Tonsillectomy	162		1.0	34	1.9***
Adenoidectomy	94		1.1	15	1.6
Circumcision	249		1.1	28	1.1
Hernia repair	123		1.0	16	1.1
Attended birth follow-up clinic	1045		1.0	141	1.2
Not seen at home by HV < 6 months	464		0.9	53	0.9
Never been to child health clinic	492		0.7***	85	1.1
Never been to dentist	1475		0.9***	245	1.1*
Immunised against pertussis	7280		1.1***	805	1.0
Immunised against measles	—		—	450	0.9
BCG	450		0.9	—	—

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

bronchitis and pneumonia developing in association with the infection. There was no evidence (Golding *et al.*, 1984) for an increase in mental subnormality after immunisation against measles.

#### BCG Immunisation

Extensive experience has apparently shown that BCG is one of the safest vaccines (*British Medical Journal*, 1980). Currently, in Britain, BCG vaccination is offered to 10–13-year-old school children. A small number of children are immunised as neonates if one member of the family has a history of tuberculosis, or when the child is thought to be at risk of contact with tuberculosis (e.g. Asian immigrant family). BCG should not be given to infants who have shown signs of eczema (Valman, 1980b).

Only 868 study children had received a BCG vaccination by the time they were 5. Epidemiologically, these children differed from those who had had the other immunisations considered above. Presumably this was because the decision is largely made by health professionals in response to a risk, rather than by the mother herself. Approximately half (473) of the children involved had had the vaccination during the first week of life.

The most dramatic association was with region (Fig. 20.5b). A quarter of all Scottish children had had a BCG by the age of 5. No other region had given BCGs to even as many as 10% of their children, and in areas in southern Britain less than 3% of children were involved.

Obviously, the regional pattern reflects, to a certain extent, areas in which tuberculosis has a higher prevalence. The same is true of the type of neighbourhood. Though rare, pulmonary TB is more common in urban, as opposed to rural, areas, and is relatively common in poor urban areas. Some 14% of children from poor urban areas had had a BCG compared with 4.3% from rural areas (Fig. 20.7).

There were no differences in BCG rates with the number of

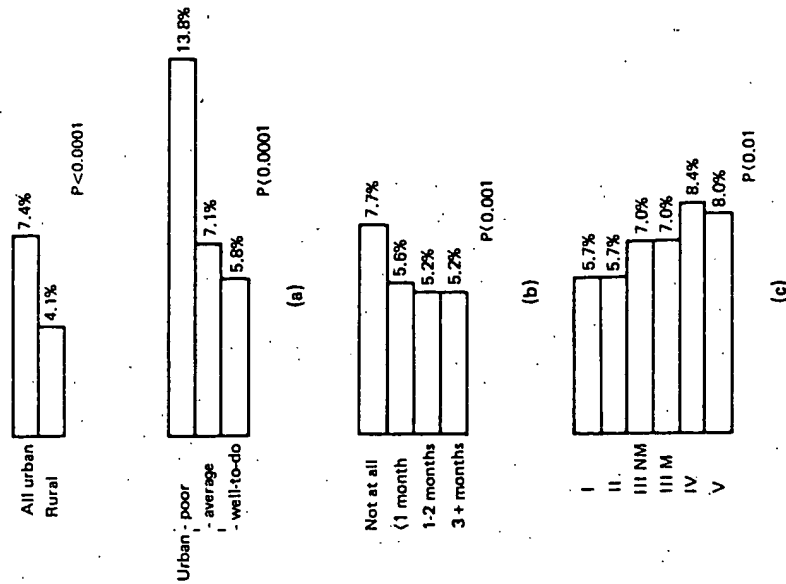


FIG. 20.7 Proportion of children receiving BCG by (a) type of neighbourhood, (b) duration of breast feeding, (c) social class (continued on next page)

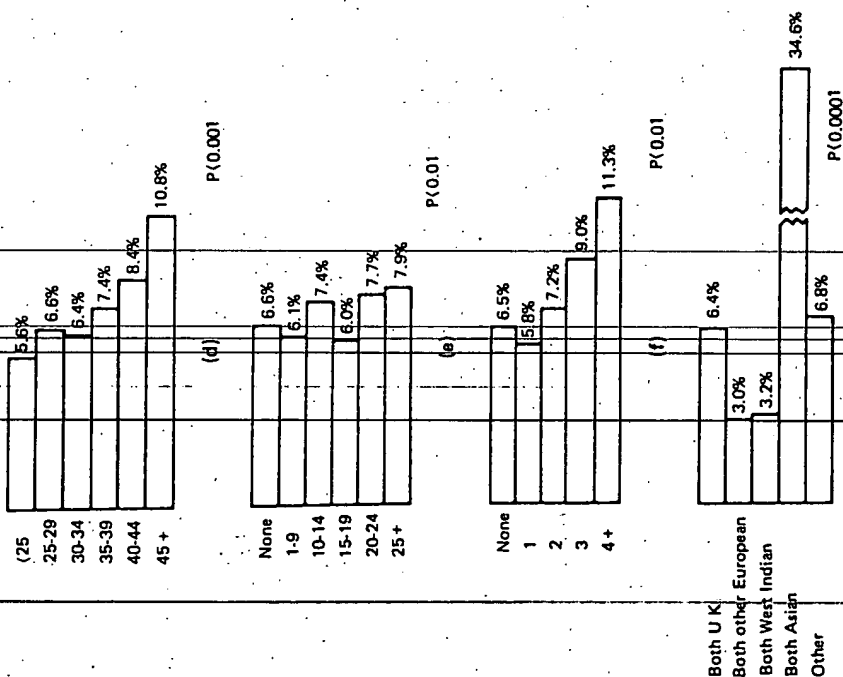


FIG. 20.7 continued (d) maternal age, (e) maternal smoking habit, (f) number of other children in the household, (g) ethnic group of parents

household moves. Boys were as likely as girls to receive the vaccine, and birthweight did not appear to affect the uptake. Children given BCG were, however, less likely to have been breast fed (Fig. 20.7). This finding was due to the predominance of Scottish children among those who had received BCG—the Scots being unlikely to breast feed their children (Chapter 4).

Children from social classes IV and V were more likely to receive BCG, as were children of mothers who were in their 40s, and those who smoked heavily (Fig. 20.7). All these associations were slight, however, in

comparison with the regional and neighbourhood differences we have shown above.

In addition, there was an association between the likelihood of a child receiving a BCG and the number of siblings in the household (Fig. 20.7). The children who had three or more siblings were more likely to have received a BCG.

The other dramatic variation was shown with ethnic group (Fig. 20.7). Over a third of children of Asian parents had had a BCG. In comparison, children of other immigrant parents had a rate of vaccination less than half that of the children of the indigenous population.

Standardisation showed that the major factors independently associated with BCG being given to a child in the pre-school years are: the area of Britain; the type of neighbourhood; the ethnic group of the parents; and the age of the mother (Fig. 20.8). Over and above these there were no significant associations with social class, parental smoking habit, duration of breast feeding or the number of other children in the household.

The health and behaviour of children who had had a BCG differed little from the rest of the population, apart from the fact that the BCG children were more likely than expected to have had a tonsillectomy (Table 20.4). In spite of the recommendation that children with infantile eczema should not be vaccinated, by the age of 5 the number of vaccinated children with a history of eczema was equal to expectation. This could mean that no attention was paid to contraindication, or it could be that although children with infantile eczema were not given a BCG, the vaccine itself was associated with the onset of eczematous lesions.

## Discussion

Finally, it is important to point out the obvious. In assessing the health and behaviour of children who have, or have not been immunised, we have ignored the diseases for which the immunisations were carried out. There was considerable morbidity, and even mortality, attached to each.

One child had died suddenly at 11 weeks during an attack of whooping cough, a boy with Down's Syndrome died at 9 months during an attack of measles, and the 5-year-old daughter of Asian parents died of diphtheria.

Four children had had tuberculosis. Three of these had pulmonary TB and were kept in hospital for up to 9 months. The fourth child was born to an Asian mother. At the time of his delivery, the mother was found to have TB. The child was kept in hospital and treated for 4 months, and returned the following year with a TB cyst in his neck.

benefit most from it. They tend to come from large families and poor urban areas where infection is passed around more easily.

### Conclusions

1. Children who were never immunised against pertussis differed from the rest of the population in that they were more likely to live in urban areas—especially the 'poor' and 'average' urban areas. The more children in the family, the less likely was the child to have been immunised. Similarly, the more cigarettes the mother smoked, the less likely was the child to have been immunised. There were strong regional differences.
2. Uptake of measles immunisation also varied with region and with type of neighbourhood: children resident in poor urban areas were less likely, and those in well-to-do urban areas were more likely, to have been immunised. Again, the more cigarettes the mother smoked, and the more children in the household, the less likely was the study child to have been immunised against measles.
3. BCG was received by a quarter of all Scottish children, but less than 6% of the rest of the country. Rural residents were least likely to receive BCG and those from poor urban neighbourhoods were most likely to do so. The older the mother, the more likely the child was to have had the vaccination. A third of the children of Asian parents had had a BCG by the age of 5.

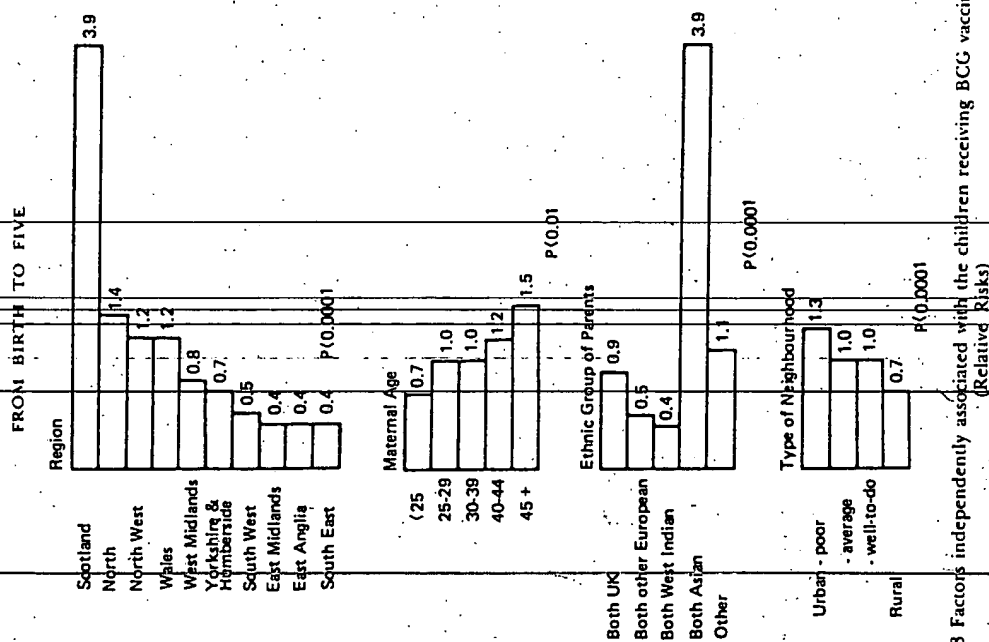


FIG. 20.8 Factors independently associated with the children receiving BCG vaccination (Relative Risks)

There were twenty children admitted to hospital with measles, and forty with pertussis. As already mentioned, these children had a high incidence of convulsions and many of those with pertussis were subsequently found to be intellectually backward. Whether this association was causal must await further study. It is, however, obvious from the data presented here that the costs and benefits of the immunisation programme are weighted heavily in favour of immunisation. It is, therefore, worth noting that the children who are least likely to be given most types of immunisation are generally those who would probably

U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon Press Canada Ltd., Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, Hammerweg 6, D-6242 Kronberg, Federal Republic of Germany
JAPAN	Pergamon Press Ltd., 8th Floor, Matsuo Central Building, 1-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160, Japan
BRAZIL	Pergamon Editora Ltda., Rua Eça de Queiroz, 346, CEP 04011, São Paulo, Brazil
PEOPLE'S REPUBLIC OF CHINA	Pergamon Press, Qianmen Hotel, Beijing, People's Republic of China

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MAR 20 1987

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First edition 1986

Library of Congress Cataloging in Publication Data

From birth to five.

Includes bibliographical references.

1. Children—Diseases—Great Britain—Longitudinal  
studies.

2. Children—Mental health—Great Britain—Longitudinal  
studies.

3. Child health services—Great Britain—Utilization.

4. Preventive health services—Great Britain—Utilization.

5. Health surveys—Great Britain.

I. Butler, Neville R. II. Golding, Jean.

RJ 03.G7H76 1985 362.1'9892/000941 85-19212

British Library Cataloguing in Publication Data

From birth to five: a study of the health and behaviour of  
Britain's five-year-olds.

1. Child development—Great Britain

2. Children—Care and hygiene—Great Britain

I. Butler, N. R. II. Golding, Jean III. Howlett, Brian  
155.4'22 BF721

ISBN 0-08-032692-7 (Hardcover)

ISBN 0-08-033372-9 (Flexicover)

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

## Acknowledgements

The work involved in mounting and carrying out a sweep of a cohort study such as this one involves a considerable number of people, not only in tracing and interviewing the parents, and examining the children, but also in coding the results, putting the coded data onto computer and analysing the final edited information. None of the present work would have been possible, were it not for the generous financial support received from the Medical Research Council, the Social Science Research Council, the National Research Council, the Action for the Crippled Child, the Rowntree Trust and many other independent trusts.

We are particularly grateful to the Area Nurses (Child Health) of the Area Health Authorities of England and Wales, together with the Nursing Officers in the Scottish Health Boards. It was their administration and the cooperation of their Health Visitors who helped to trace the study children and carry out the survey. We are also extremely grateful for the collaboration of the Health Visitors Association who were co-sponsors of the study. In addition, the National Health Service Central Register and the Family Practitioner Committees of England and Wales together with the Administrators of Primary Care in Scotland and their colleagues in the Health Authorities/Boards assisted in locating the whereabouts of the children.

The huge amount of clerical work involved in the administration of the survey and the coding of questionnaire data called for enormous patience and fortitude. We were fortunate in finding these qualities in Sylvia Zair who supervised the coding process and our principal clerical workers Pam Lyons, James Parsons, Britta Pendry, Mary Probert and Sheila Taylor. The principal scientific officers who designed and organised the 5 year sweep were Professor N. R. Butler, Dr. Sue Dowling, Mr. B. Howlett and Mr. A. Osborn.

The actual preparation of the present volume would have been impossible without the willing and enthusiastic assistance of personnel currently working on the project including: Yasmin Iles, Penny Hicks, Tim Sladden, Mary Paterson, Michael Mack, Valerie Duffield, Michael Johns, Jean Lawrie, Andrew Bernard and Ian Collier.

To all, we offer our sincere thanks, but especially to the mothers and children of the cohort.

# Child Health and Education Study

This was a national longitudinal study of children born during the week 5-11 April 1970 in England, Scotland and Wales.

The children in this survey were originally subjects of the British Births survey carried out in 1970 under the auspices of the National Birthday Trust Fund and the Royal College of Obstetricians and Gynaecologists.

The 1975 follow-up survey was carried out by the Department of Child Health, University of Bristol, under the directorship of Professor Neville Butler and with the collaboration of the Health Visitors Association.

## The Director

Professor Neville Butler, MD, FRCP, FRCOG; DCH was Professor of Child Health at the University of Bristol consultant to the World Health Organisation and to the Pan-American Health Organisation. His work with British child development studies began in 1958 when he was Director of the Perinatal Mortality Survey.

## Principal Research Officers in 1975

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Social — Albert Osborn, BA, PhD  
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Statistics — Anthony Morris, BA, MSc

Dr. Sue Dowling is currently lecturer in Epidemiology and Community Medicine at the University of Bristol.

XXVII

## CHAPTER 1

# Introduction

by JEAN GOLDING and N. R. BUTLER

Life progresses forward in time, but, as Kierkegaard said, we only understand in retrospect. Thus in individual persons we wait for an abnormal facet of health or behaviour to occur and then search back through time for factors on which we may pin responsibility. In any one life, there are a multitude of interwoven events and influences, but those that we choose to consider as causative are likely to conform to the received wisdom of our generation. Thus, we are now likely to associate our neurotic behaviour with an authoritarian upbringing, our child's asthma with our own stress. Search for explanations in individual cases is natural. Determination of an acceptable cause is consoling, but rarely capable of rigorous proof. Nevertheless, it is important that we have a firm foundation on which to link events together. Belief is not enough. After all, whole populations in the Middle Ages were convinced that women who gave birth to severely malformed infants were guilty of witchcraft. Can we be certain that the associations that we tend to accept now are any more valid?

Studies of single individuals can rarely help answer this question, but a long-term study of a larger population can aid considerably. Nevertheless, it must always be remembered that an epidemiological study can only rarely provide positive proof of the 'cause' of an event—rather it will suggest guilt by association. Such studies can, however, point the way to fruitful areas for more detailed investigation—and occasionally they may provide clues for primary prevention of a disorder even though the understanding of the mechanism of the genesis of that disorder may be years away (the association between smoking and cancer of the lung is an obvious example).

## Historical Background

Since 1946 there has been a unique tradition of national longitudinal cohort studies in Britain. The first study was mounted in the immediate postwar period because it was felt that little sound knowledge was

available concerning the social and economic aspects of pregnancy and childbirth. The then College of Obstetricians and Gynaecologists and the Population Investigation Committee initiated a survey designed to assess: (a) the availability of the maternity services to different social classes and in different parts of Great Britain; (b) the use made of these services; (c) their effectiveness in educating mothers and in reducing mortality and morbidity among mothers and infants; (d) the need for domestic help during pregnancy and after delivery; (e) the nature and extent of parental expenditure on childbirth.

To obtain data on sufficient numbers for valid analysis, a survey was carried out of all births in England, Scotland and Wales in 1 week. For administrative rather than scientific reasons the week chosen was that of 3-9 March 1946. The mothers were interviewed by their health visitor some 8 weeks after delivery. The conclusions and recommendations of this study were far-reaching in their implications and, interestingly, are still largely pertinent today (*Maternity in Great Britain 1948*). They emphasise the need for the maternity services to cater for the physical and psychological well-being of the mother, as well as for the medical requirements of both mother and infant. The last of thirty-four recommendations suggested that childbirth should not be regarded solely as an event relevant to mother and baby for only a short period of time, but rather as an occasion with potential effects which might not become apparent until much later in the child's or mother's life. It was for this reason that it was decided to follow up the cohort first at the age of 2 years and subsequently a sample has been contacted at frequent periods ever since (*The National Survey of Health and Development*). The results of the study of this cohort have been of importance in the educational, sociological and psychological fields (Douglas and Blomfield, 1958; Douglas, 1964; Douglas *et al.*, 1968). Among other findings, it has been responsible for showing an association between prolonged or repeated hospital admission in early childhood and later behavioural and learning problems (Douglas, 1975), that disruptions of early family life were strongly associated with delinquent behaviour in adolescence (Wadsworth, 1979), that children who had pneumonia or bronchitis in the first 2 years of life were more likely to have a chronic cough at the age of 25 (Kiernan *et al.*, 1976) and that serum cholesterol of 32-year-old males was lower in those that had been breast fed (Marmot *et al.*, 1980). The first survey has now started to collect information on the offspring of the children in the original sample, and the study of intergenerational differences is uniquely fascinating. For example, Kiernan (1980) has shown that the girls in this cohort who became pregnant in their teens had parents who had themselves married early, and who had relatively low levels of education.

The second cohort, like the first, devolved from a study of the

perinatal period (*The Perinatal Mortality Survey*). The initial 1958 birth survey had somewhat different ends in view from those of Douglas in 1946. Undertaken by the National Birthday Trust Fund, it was initiated in 1958 because, in the postwar period the perinatal mortality rate had remained fairly static (3.85% in 1948, 3.51% in 1958), although the maternal and childhood mortality rates had fallen dramatically. For this reason, the survey was designed specifically to examine the individual causes of perinatal deaths.

It was designed in two overlapping parts: the first was concerned with all deliveries in the United Kingdom in the week of 3-9 March 1958. For each birth a questionnaire was filled in by the midwife shortly after delivery. Information was obtained on social background, history of pregnancy, delivery and the neonatal period partly from obstetric notes and partly by interviewing the mother. The second part of the survey was concerned with all stillbirths and neonatal deaths in the 3 month period of March, April and May 1958. For the majority of these, detailed post-mortems were carried out. The questionnaire on the maternal background, pregnancy and delivery was also completed for all these deaths. Details of 7117 still births and neonatal deaths were compared with 17,204 total births occurring in the 1 week (Butler and Bonham, 1963; Butler and Alberman, 1969).

The results of this survey were used widely by obstetricians, paediatricians, midwives, general practitioners and others. The survey showed that it was possible to predict which women were at highest risk of having a stillbirth or neonatal death. A comparison of the ways in which the obstetric services varied throughout the country resulted in the rethinking of many obstetric procedures, the reorganisation of obstetric practice and the stimulation of further research (Peel, 1969). Whether or not this survey was directly responsible, the perinatal mortality rate fell dramatically from 1958 onwards.

Again, it was something of an afterthought that this survey of obstetric practice was expanded into a follow-up to embrace child development (*The National Child Development Study*). Those children born in that 1 week in March who had survived were traced when they were 7 years old: medical and social histories were taken; medical examinations were performed; and the children underwent a number of educational tests. They have been contacted also at the ages of 11, 16 and 21, and much valuable information has accrued. An important fact to emerge is that children from disadvantaged backgrounds differ not only in reduced physical stature and increased prevalence of medical problems, but also in difficult behaviour and poor educational attainment (Davie, Butler and Goldstein, 1972). On a more optimistic note, there was little to suggest that traumatic events of pregnancy and delivery had any long-term effects provided the child survived the perinatal period.

Several studies from this data-base have found associations between smoking during pregnancy and reduction in birthweight, increased perinatal mortality rate, and some reduction in the child's subsequent height and educational attainment (Butler *et al.*, 1972; Butler and Goldstein, 1973; Fogelman, 1980). A further hypothesis was generated from the finding that children of women who had reported having 'flu in pregnancy were at increased risk of developing cancer (Fedrick and Alberman, 1972). This has prompted a large number of prospective studies in various parts of the world on the possible effects of infection in pregnancy. Other interesting points have been found in the comparison of the two cohorts: for example, the children born in 1958 were far less likely to undergo tonsillectomy or circumcision than those born in 1946 (Calnan *et al.*, 1978), though the later cohort was much more likely to develop diabetes. (Calnan and Peckham, 1977).

#### The 1970 Cohort

The third national cohort study and the survey on which the present report is based again began primarily as a study of the perinatal period. It was carried out by the National Birthday Trust Fund in association with the Royal College of Obstetricians and Gynaecologists and is known as the *British Births Survey*. Its aims were to look at the obstetric services and the social and biological characteristics of the mother in regard to neonatal morbidity, and to compare the results with those of the 1958 study. As in the two previous surveys, a week of deliveries was studied, that chosen being the period 5-11 April 1970. A questionnaire was filled in by the midwife, after interviewing the mother and having access to the clinical notes. This survey provides a valuable glimpse into the patterns of obstetric and neonatal care in the United Kingdom in 1970 (R. Chamberlain *et al.*, 1975; G. Chamberlain *et al.*, 1978).

The first follow-up of survivors from this survey occurred at the age of 22 months and comprised (a) the twins, (b) the small-for-dates and postmature and (c) a 10% random sample of all legitimate births. A medical and developmental history was completed by the health visitor, and the child was not only examined medically and measured, but also completed some simple developmental tests. The same subsamples were seen at 3 years and subjected to medical examination and developmental tests appropriate for their chronological age. The data thus obtained have shown the prevalence of illness in early infancy (Chamberlain and Simpson, 1979), the development of children aged 22 months (Chamberlain and Davey, 1976) and the differential growth of the subsamples (Chamberlain and Davey, 1975).

The disadvantage in using relatively small samples is that in any

analysis of a particular type of illness or behaviour problem the numbers are often too small for valid conclusions to be reached. For this reason it was decided early in 1973 to attempt to contact the whole population of children born in this 1 week of 1970 at around their 5th birthday. The Medical Research Council provided the funding for the central organisation and administration of the study, but all the field-work relied on the voluntary co-operation and enthusiasm of the local health visitors.

#### Tracing the children

The population we wished to study was defined solely by date of birth. In this way we hoped to identify the estimated 2% of children whose births had not been recorded in the original birth survey, as well as those children who had been born outside Great Britain but were resident in Britain by the age of 5 years. The original birth survey had included births in Northern Ireland, but by 1975 it was felt to be too sensitive an area to be included. Therefore, only those eleven children born in Northern Ireland, but subsequently resident in England, Scotland and Wales, were included in the 5-year cohort.

In order to trace the whereabouts of the population, the Office of Population Censuses and Surveys (OPCS) generated a computer-listing of all children registered as having their date of birth in the sample week. This list was sent to the National Health Service Central Register (NHSCR) at Southport, who were able to identify either the Area Health Authority in which the child was registered with a general practitioner, or whether the child had gone abroad or died. From the details given, a list of children believed to be living in each Area Health Authority was sent to the appropriate Family Practitioner Committee who was able to identify the child's current address. This information was passed by the Family Practitioner Committee to the Area Health Visiting Service, which then contacted the parents of the child and invited them to participate in the study.

A similar procedure was adopted in Scotland, although the Scottish records were unable to yield information on those children born in the survey week who had not been included in the original birth survey. Children of servicemen who were registered with a Service Medical Officer were traced with the help of the Service Children's Education Authority.

A further method of ascertaining the study population was also attempted as a fail-safe mechanism, by asking all health visitors throughout Britain to go through their files to identify children born in the study week but not yet traced.

### Administering the questionnaires

Once the child had been traced, and the parents agreed to participate, a health visitor arranged to call. She interviewed one or both of the parents (usually the mother alone) by means of a structured questionnaire (the Home Interview Questionnaire, reproduced on pages 379-398). This included detailed information on the child's medical history as well as the social and family background.

A second questionnaire (the Maternal Self-Completion Questionnaire, reproduced on pages 399-406) had been designed for the mother to fill in on her own, so that any biases introduced by the interviewer could be minimised. The information was concerned largely with the mother's perception of her child's behaviour, as well as of her own well-being. On the same occasion, measures of the child's general development were obtained using a specially designed Test Booklet, and the health visitor measured the child's height and head circumference.

Lastly, a questionnaire entitled the Developmental History Schedule was completed on the study child by the health visitor herself with the help of her own child health clinic records. Information was sought on all attendances at child health clinics and visits by the health visitors in the first 5 years, on perinatal and subsequent risk factors and inclusions on registers, as well as results of all screening and assessment procedures.

### Case ascertainment

In all, 13,961 children were traced: i.e. an estimated 85.8% of the population at risk (Table 1.1). Of these, 631 parents refused permission for their child to take part and 195 were not included either because, in spite of repeated efforts, the health visitor was unable to arrange an interview, or because the information obtained was incomplete. A total

TABLE 1.1 Results of attempt to trace and interview the population of children born 5-11 April at age 5

All children born in England, Scotland and Wales and included in British Births Survey (BBS)	16,567	
No. of those stillborn or known to have died before follow up was possible	563	
No. thus assumed alive at 5	16,004	
No. of the above surveyed at 5	12,732 (79.6%)	
Surveyed at 5 in BBS, but born in Northern Ireland	11	
Surveyed at 5, but not in BBS	392	
Total surveyed at 5	13,135	

of 13,135 sets of completed forms (i.e. Home Interview Questionnaire, Maternal Self-Completion and Test Booklet) were received. The total yield of Developmental History Schedules was less, since often the clinic and health visitor notes were absent or incomplete. Nevertheless, by the end of the 5-year study, over 10,000 completed schedules had been received.

In order to establish the extent to which the sample of 5-year-olds was biased, we have compared the proportion of children surveyed at 5 years of age according to various items of information collected at their birth (Table 1.2). The children for whom questionnaires were *not* filled in at 5 years were slightly more likely to be of low gestation and/or birthweight, and to have mothers who smoked heavily. The major difference, however, was in the marital status of the mothers: only 59% of those children with unmarried mothers at the time of birth were included in the survey at 5 years of age, compared with 81% of those whose mothers were married.

A further exercise, undertaken when the children were 7, attempted to trace those children not included in the 5-year cohort. By this time, of course, all the children were at school and the tracing of the birth cohort was a relatively easy exercise, facilitated by the education record system. For the 1917 new children contacted, a simple questionnaire on parental circumstances and certain aspects of medical history was filled in. Comparison of the events of the first 5 years of these children's lives (Osborn *et al.*, 1984) revealed that those who had not been traced at 5 years were far more likely to be living apart from their natural father, to have either Asian parents or parents of mixed race, to have moved house at least twice and to have been 'in care'.

In spite of these differences, and notwithstanding their statistical significance, the bias caused by omission of these children is unlikely to have a profound effect on the overall results we are presenting here. Where potential bias may exist, it will be fully discussed.

### The Present Report

In this volume we shall describe the health and behaviour of the study children in the first 5 years of their lives. The first chapters present a description of the social and environmental background of the families, and subsequent chapters analyse those factors which may influence the prevalence of the various behaviour traits, signs or symptoms in the child. In later sections we shall indicate the environmental and social characteristics of families who appear not to use the health services to their full advantage.

In order to define clearly the remit of our study, we have examined the epidemiological associations between various health outcomes in the

TABLE 1.2 Proportion of the surviving children born in Great Britain and appearing in the British Birth Survey who were surveyed at 5 (singletons only)

Factor at birth	Proportion surveyed	%
Social class: I and II III M and III NM IV and V	2012/2502 7150/8673 2547/3216	(80.4) (82.4) (79.2)
Mother's age: < 20 20-34 35+	1105/1536 10,266/12,703 982/1258	(71.9) (80.8) (78.1)
Parity: 0 1 2-3 4+	4648/5886 4169/5100 2891/3655 357/1026	(79.0) (81.7) (79.1) (73.8)
Maternal smoking: non-smoker stopped pre-pregnancy stopped during pregnancy < 15 per day 15+ per day	5214/6562 1571/1894 596/747 3487/4368 1574/2061	(79.5) (82.9) (79.8) (79.8) (76.4)
Marital status: married single separated, widowed, divorced	11,788/14,528 493/869 181/271	(81.1) (56.7) (66.8)
Sex of child: male female	6457/8091 6019/7593	(79.8) (79.3)
Time to regular respirations: < 3 min 3 min+	11,905/14,944 498/647	(79.7) (77.0)
Birthweight: < 5 lb 8 oz 5 lb 8 oz+	580/767 11,885/14,902	(75.6) (79.8)
Gestation: < 37 37+ unbelievable/unknown	404/529 9678/11,949 2394/3207	(76.4) (81.0) (74.6)

child and fourteen variables: sex of the child; birthweight; duration of breast feeding; maternal age; social class; parental situation when the child was 5; ethnic group of parents; maternal and paternal smoking habits; maternal employment history during the child's life; number of other children in the household; number of times the child moved house; the type of neighbourhood and region in which the child lived.

Obviously, there is a massive body of statistical data which, for reasons

of space and price, must be excluded from this volume. All the many hundreds of tables used in compiling this report have therefore been deposited with the British Lending Library, Boston Spa, Wetherby, West Yorks LS23 7BQ, UK. To obtain a copy, write to the British Lending Library requesting Supplementary Publication No. 90, 119 (958 pages). Identification of particular tables may be made using the index to this volume. In general, all significant results will be referred to fully in the text and illustrated with the aid of simple diagrams.

With such a large amount of information trivial differences are often statistically significant at the 5% level. We have, therefore, only considered associations to be statistically significant if the probability that they might have arisen by chance was less than 0.01 (i.e. 1%). Nevertheless, it is important to recognise that on average one in a hundred of our results will be significant by chance—i.e. they will indicate an association that is not really present. How can one detect such misleading findings? In examining the validity of any association, evidence that it is not spurious can only be obtained if confirmatory evidence is available from reports in the literature. In all other cases care must be taken to verify the results in other studies before associations are accepted as real.

There are other ways in which associations may be misleading initially, but from which statistical analysis can assist in interpretation. Consider, for example, a disease X. Suppose that the prevalence of this disease varies with social class, such that children in the upper social classes are at only half the risk of the disorder compared with those in the lower social classes (Fig. 1.1a).

Imagine then that prevalence by maternal age was also statistically significant: the younger the mother, the more likely the child to have had the disorder (Fig. 1.1b).

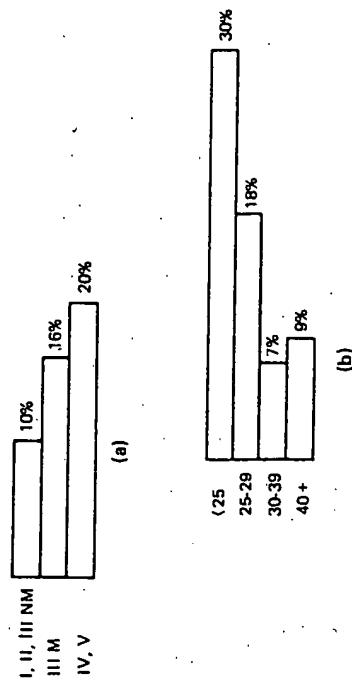


FIG. 1.1 Hypothetical prevalence of disease X by (a) social class, (b) maternal age

Within Britain, mothers from the lower social classes are, in general, younger than those from upper social classes. The findings illustrated in Figs. 1.1a,b could be the result of three possible eventualities: (a) the disease X is strongly associated with a lower social class and because the lower social classes are younger, the pattern in Fig. 1.1b was bound to result; (b) the disease X is strongly associated with youthful mothers, and since very young mothers are mostly from the lower social classes, the pattern of Fig. 1.1a was bound to result; (c) disease X is strongly and independently associated with both youthful maternal age and low social class.

In order to distinguish between these three possibilities, various statistical methods are possible. We have actually used indirect standardisation, a method which is described more fully in the Appendix (pages 356-7). The results of such standardisation are given in terms of observed and expected numbers, and published in the microfiche Appendix tables. Associations that are still statistically significant are given as Relative Risks. These are easy to interpret: a Relative Risk of 1.0 means that the chance of the outcome in that particular group is equal to the risk of the whole study population; a risk of 2.0 is twice that of the whole population; but 0.6 is only 60% of the population risk.

Relative Risks computed in this way can be extremely useful in estimating the prevalence of a disorder in a closely defined sub-population. Suppose, for example, that standardisation on the data depicted in Figs. 1.1a and 1.1b revealed that both social class and maternal age were independently associated with disease X in the way depicted in Fig. 1.2. This shows that children of social class I have only

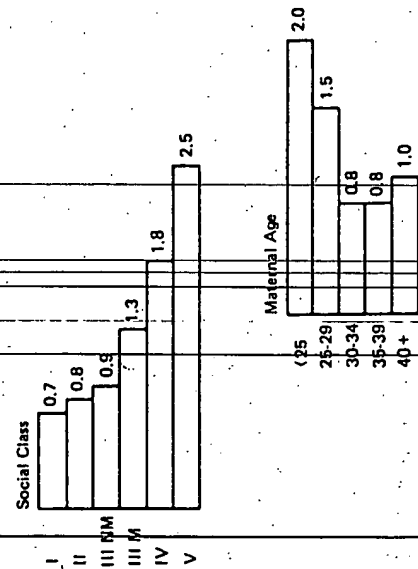


FIG. 1.2 Hypothetical independent Relative Risks of disease X

70% of the risk of the population as a whole, whereas social class V has two-and-a-half times the risk. Suppose the health profession wished to ascertain the risk to a population of mothers aged under 25 of social class IV. The estimate takes the relative risk to the child in social class IV (i.e. 1.8), and that to the child of the young mother (2.0) and multiplies the risks together. The risk to children in this sub-population will be approximately 3.6 times the population average.

Obviously, with so much information, and the complex inter-relationships between the child's health and behaviour, his parents and his geographical environment, we have been able to do little more than skim the surface. The data presented form a fascinating glimpse into the factors which do and do not appear to influence the child's health and behaviour. We hope that some of our results may prompt in depth studies to help unravel or confirm our findings. Child health is not static, and the most exciting projects await our research team as we watch the children in the cohort grow and develop. As they navigate problems, some will flounder, and others will toss off the difficulties.